medulloblastomas and other M+/MO tumors.

Remarks

Claims 18-25 are active. All claims have been rejected. Applicants traverse all rejections in the light of the amendments above, the remarks below, and state-of-the-art references to support the traversals.

Applicants acknowledge the finality of the restriction requirement.

The Abstract has been appropriately shortened.

Typographical errors have been corrected.

Claim Rejections

35 USC 112 (1)

The examiner has rejected claim 18-25 on an allegation that the specification does not disclose results with a "subject" and that cell culture methods used in the invention cannot predict the effects of the inhibitors *in vivo*. The examiner provides only a single reference (Collett et al.) to support his position. Applicants traverse this rejection on the following bases:

1. With respect, applicants submit that the examiner has misquoted Collett *et al.* On p. 819, left column, under Conclusions, the authors state:

"The increase in A-B drug permeability following inhibition of PGP in Caco-2 allows a reasonable prediction of the likely in vivo impact that PGP will have on plasma drug levels after oral administration."

The examiner is reminded that Caco-2 refers to cells in monolayer tissue culture.

In addition, in Collett *et al*, p. 825, left column, the authors state:

"In conclusion, the current study...has established a quantitative relationship between PGP-induced changes across Caco-2 and PGP-induced decreases in plasma concentrations of orally administered drugs in mice."

Thus, contrary to the examiner's assertion, Collett *et al.* does not support his position, but rather strengthens applicants' argument that the studies using Daoy human medulloblastoma cells in culture serve as a model for the results in animals and humans.

2. The examiner is also respectfully referred to the first paragraph on p. 9 of the specification, where it is stated that the Daoy human medulloblastoma cell line was

selected because it closely resembles human tumors genetically. Of the 30,000 genes in the Daoy cell line, 98% were also present in the human solid tumors studied. This indicated that, genetically, this cell line is as close as one can get to humans. An animal model will not help to prove if the present hypothesis is valid, as metastasis in mice does not mimic that in humans.

3. Limitations of animal models and the preferability of tissue culture cells for some studies are described in Nature Biotechnology 16:100-101 (1998); a copy is enclosed. The examiner will note at the top of the middle column on p. 100 the statement:

"...many of the key disease events, such as metastasis, did not occur in the xenograft models limiting the predictive value of this approach. To overcome this limitation, the next step was to develop human cancer cell lines."

The examiner will have noted, of course, that the Daoy cells used by the present inventors are derived from a human medulloblastoma tumor.

4. The two papers from John M. Weinstein, MD, PhD and Michael R. Boyd, MD PhD of the National Cancer Institute (copies enclosed) describe the NCI-directed effort to screen for potential drug targets using a panel of 60 *cell lines* representing different human cancers. The articles describe the success and validity of such an approach.

5. Finally, applicants wish to remind the examiner of the findings of the Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). On bridge paragraph, pp4/5, the Court states:

"The ... cell lines, although technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the ... cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice."

And on p. 5, first full paragraph:

"We conclude that these tumor models represent a specific disease against which the alleged compounds are said to be effective."

For all of these many and sufficient reasons, it is clear that the examiner has not offered any support for his decision, and that the scientific literature totally supports applicants' position. The examiner is therefore urged to withdraw these rejections.

<u>35 USC 102(b)</u>

Claims 18, 20-22 are rejected as being anticipated by Zujewski *et al.* Applicants traverse these rejections.

As the examiner knows well, in order to anticipate a reference must contain within its four corners all of the elements of the claim being attacked. For one thing, Zujewski discloses only FDA-required Phase I toxicity studies with a farnesyl transferase protein inhibitor; no effects on human tumors were reported.

In sharp contrast, the thrust and main target of the present invention is the gene for the Platelet Derived Growth Factor Receptor Alpha (PDGFRA) which is upregulated in many human tumors (i.e., M+), including medulloblastomas. This thrust is disclosed in the Summary of the invention, in all drawings, throughout the description of the preferred embodiments and examples, and in the original claims. The other genes mentioned in the claims, including the RAS/MARK gene that is located downstream of the PDGFRA gene, are simply genes through which the PDGFRA gene operates. Claims 26 and 27 have been added to reinforce this point.

In addition, Zujewski does not disclose all of the elements of generic claim 18, as amended. No new matter is involved in amended claim 18. All of the elements were present in the claims as originally filed.

Thus, the Zujewski *et al.* reference cannot be said to anticipate the present claims, and rejections over this reference should be withdrawn.

35 USC 102(e)(2)

Claims 18-21 and 23-25 have been rejected as anticipated by Daley. All rejections are traversed.

Daley is irrelevant. The reference discloses solely the use of inhibitors of solely farnesyl protein transferase. This is not an element of any of the present claims. Further, Daley does not disclose all of the elements of amended generic claim 18. Hence, Daley cannot be said to anticipate any of the present claims.

These rejections should be withdrawn.

Conclusion

For these many and sufficient reasons, all rejections of claims should be withdrawn, and all claims should be allowed.

Respectfully submitted,

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